PATENT COOPERATION TREATY

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INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY
(Chapter I of the Patent Cooperation Treaty)

(PCT Rule 44*bis*)

Applicant's or agent's file reference SDUC1160WO	**FOR FURTHER ACTION**	See item 4 below
International application No. PCT/US2004/036456	International filing date *(day/month/year)* 01 November 2004 (01.11.2004)	Priority date *(day/month/year)* 05 November 2003 (05.11.2003)
International Patent Classification (8th edition unless older edition indicated) See relevant information in Form PCT/ISA/237		
Applicant THE REGENTS OF THE UNIVERSITY OF CALIFORNIA		

1. This international preliminary report on patentability (Chapter I) is issued by the International Bureau on behalf of the International Searching Authority under Rule 44 *bis*.1(a).

2. This REPORT consists of a total of 7 sheets, including this cover sheet.

   In the attached sheets, any reference to the written opinion of the International Searching Authority should be read as a reference to the international preliminary report on patentability (Chapter I) instead.

3. This report contains indications relating to the following items:

☒	Box No. I	Basis of the report
☐	Box No. II	Priority
☐	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☒	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☐	Box No. VIII	Certain observations on the international application

4. The International Bureau will communicate this report to designated Offices in accordance with Rules 44*bis*.3(c) and 93*bis*.1 but not, except where the applicant makes an express request under Article 23(2), before the expiration of 30 months from the priority date (Rule 44*bis* .2).

	Date of issuance of this report 08 May 2006 (08.05.2006)
The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Authorized officer Masashi Honda
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Form PCT/IB/373 (January 2004)

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:
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P.O. BOX 80278
SAN DIEGO, CA 92138-0278

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing *(day/month/year)*	27 JUN 2005
Applicant's or agent's file reference SDUC1160WO	FOR FURTHER ACTION See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US04/36456	01 November 2004 (01.11.2004)	05 November 2003 (05.11.2003)

International Patent Classification (IPC) or both national classification and IPC

IPC(7): G06F 19/00 and US Cl.: 702/27

Applicant

REAGENTS OF THE UNIVERSITY OF CALIFORNIA

1. This opinion contains indications relating to the following items:

- ☒ Box No. I — Basis of the opinion
- ☐ Box No. II — Priority
- ☐ Box No. III — Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☒ Box No. IV — Lack of unity of invention
- ☒ Box No. V — Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI — Certain documents cited
- ☐ Box No. VII — Certain defects in the international application
- ☐ Box No. VIII — Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1*bis*(*b*) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA/ US	Authorized officer
Mail Stop PCT, Attn: ISA/US Commissioner for Patents P.O. Box 1450 Alexandria, Virginia 22313-1450 Facsimile No. (571) 273-8300	Eric S. DeJong EDJ Telephone No. (571) 272-6099

JOHN S. BRUSCA, PH.D.
PRIMARY EXAMINER

Form PCT/ISA/237 (cover sheet) (January 2004)

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application PCT/US04/36456

Box No. I Basis of this opinion

1. With regard to the language, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

☐ This opinion has been established on the basis of a translation from the original language into the following language _____, which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

a. type of material

☐ a sequence listing

☐ table(s) related to the sequence listing

b. format of material

☐ in written format

☐ in computer readable form

c. time of filing/furnishing

☐ contained in international application as filed.

☐ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application PCT/US04/36456

Box No. IV Lack of unity of invention

1. ☒ In response to the invitation (Form PCT/ISA/206) to pay additional fees the applicant has:
   - ☒ paid additional fees
   - ☐ paid additional fees under protest
   - ☐ not paid additional fees
2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose not to invite the applicant to pay additional fees.
3. This Authority considers that the requirement of unity of invention in accordance with Rule 13.1, 13.2 and 13.3 is
   - ☐ complied with
   - ☒ not complied with for the following reasons:

   See the lack of unity section of the International Search Report(Form PCT/ISA/210)

4. Consequently, this opinion has been established in respect of the following parts of the international application:
   - ☒ all parts.
   - ☐ the parts relating to claims Nos. _____

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application PCT/US04/36456

Box No. V Reasoned statement under Rule 43 *bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims 4-37 and 39-44	YES
	Claims 1-3, 38	NO
Inventive step (IS)	Claims 6, 8-10, 18, 20, 28-31, 36, 37, and 39-44	YES
	Claims 1-5, 7, 11-17, 19, 21-27, 32-35, and 38	NO
Industrial applicability (IA)	Claims 1-44	YES
	Claims NONE	NO

2. Citations and explanations:

Please See Continuation Sheet

Supplemental Box
In case the space in any of the preceding boxes is not sufficient.

V. 2. Citations and Explanations:
Claims 1-3 and 38 lack novelty under PCT Article 33(2) as being anticipated by Mayo et al.

Mayo et al. sets for an automated method for protein structure design and determination that relies upon establishing a set of protein structures from a given sequence, molecular dynamics modeling based on energetics, thermodynamic factors, and force field computations, and empirically established data. See Mayo et al., Figures 2, 3, and 5 and column 2, lines 22-64. One advantageous aspect put forth in the disclosed methodology is the recursive analysis of predicted structures against empirical results. See mayo et al., Example 2, column 41, line 10 through column 45, line 60. Mayo et al. do set forth that the preferred embodiment of the method is performed with a known structure as a starting point, however, it is also specifically stated that alternate embodiments exists. Further, the methodology begins with permutations to a given protein and teach away from the any limitation of performing the invention only with known structures of proteins. See Mayo et al., column 5, lines 39-59. Further, explicit consideration of amide hydrogen exchange is set forth in Mayo et al. (column 53, line 30 through column 56, line 63). Empirical amide hydrogen exchange experiments were performed using NMR spectroscopy and then compared against calculations performed with the predicted structures generated in the disclosed methodology. NMR spectroscopy performed coupled together with cryoprobe technology allows for extremely small sample concentrations (at or below 10 ug as in claim 2) for the performance of HSQC/HMQC experiments used in evaluating amide hydrogen and deuterium (as in claim 3) exchange assays in proteins. Mayo et al. further sets forth that a large number of predicted structures can be generated from the disclosed methods and analyzed against empirical data, and an example is given wherein an approximate range is extrapolated to be from 300 to 10,000. See Mayo et al., column 39, lines 13-42.

Claims 1-5, 7, 11-17, 19, 21-27, 32-35, and 38 lack an inventive step under PCT Article 33(3) as being obvious over Mayo et al. in view of either Wang et al. (J. Am. Soc. Mass. Spectrom., 1999) or Wang et al. (Biochemistry, 2001).

While Mayo et al. sets forth the above procedures for the prediction and determination of protein structures as described above, Mayo et al. does not fairly teach generating a population of sequence overlapping endopeptidase fragments of a protein labeled with a hydrogen isotope and then deconvoluting the fragmentation data. However, Mayo et al. does set forth the advantage of the disclosed methodology is the coupling together of protein modeling and prediction with empirical data in order to improve the resultant structures.

Wang et al. sets forth a structurally investigative methodology, performed on the Troponin C calcium binding protein, by the performance of H/D exchange followed by proteolytic digestion and mass spectometry to in order to localize solvent accessibility within individual peptide fragments of a protein. Pepsin digestion is specifically cited as the endopeptidase used to generate the protein fragments. See Wang et al., Abstract and page 703, column 1, line 1 through column 2, line15. The pH of the digestion reaction is performed at pH 2.2 which under a reasonably broad interpretation reads on the claimed ranges of about 1.8-3.4, about 2-3, about 2-2.5, and about 2.5-3.0 (claims 11-15). See Wang et al., page 704, column 2, Peptide Digestion. While the digestion of protein was allowed to occur on a column for 3 minutes, the completion of the reaction is determined by the concentration of protein and pepsin and it would be obvious to one of skill in the art to perform the experiment under desired condition to reach the conclusion of the reaction (claims 15-17). The temperature of hydrogen exchange experiments were performed at below room temperature and thus under a reasonably broad interpretation read on the claimed slowed exchange condition as in claim 19. Mass spectroscopy was performed on peptide fragments as claimed and further described in the Experimental description of Wang et al., page 704, column 2, last bridging paragraph through page 706, column 1, first bridging paragraph. For the purpose of this written opinion, the teachings of Wang et al. (Biochemistry, 2001) is considered cumulative with that of Wang et al. (J. Am. Soc. Mass. Spectrom., 1999).

Therefore it would have been obvious to one of skill in the art to employ the structure prediction and determination methodologies as disclosed by Mayo et al. in wherein the recursive analysis of the protein structures were evaluated using the

Supplemental Box
In case the space in any of the preceding boxes is not sufficient.

experimental assays as disclosed in Wang et al.

Claims 6, 8-10, 18, 20, 28-31, 36, 37, and 39-44 meet the criteria set out in PCT Article 33(2)-(3), because the prior art does not teach or fairly suggest the specific limitations of using more than one endopeptidase, an endopeptidase coupled to a support column, various species of endopeptidases or other methodological steps as recited in the above said claims.

Claims 1-44 meet the criteria set out in PCT Article 33(4), and thus have industrial applicability because the subject matter claimed can be made or used in industry.